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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,702	09/13/2001	Edward A. Berger	4239-60771	9274

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EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,702	BERGER ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,19,23-33,35-39,48,49 and 52-54* is/are pending in the application.

4a) Of the above claim(s) *35,36,38 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,19,23-33,37,48,49 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,19,23-33,35-39,48,49 and 52-54* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed on 3-1-2004. Claims 1, 25, 33, 37 and 55 have been amended. Claims 2-6, 11-12, 14-18, 34, 40 and 55 are canceled. Claims 35-36 and 38-39 remain withdrawn from consideration. Claims 1, 19, 23-33, 37, 48-49 and 52-54 are currently under examination.

Objections Withdrawn

Claim Objections

The objection to claim 14 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn. Cancellation of said claim has rendered the objection moot.

The objection to claim 16 for reciting inconsistent nomenclature is withdrawn. Cancellation of said claim has rendered the objection moot.

Specification

The objection to the specification for improperly reciting the trademark QIAexpress is withdrawn in light of the amendment thereto.

The objection to the specification for containing an embedded hyperlink and/or other form of browser-executable code is withdrawn in light of the amendment thereto.

Claim Rejections Withdrawn

The rejection of claims 16, 18, 34 and 37 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in light of the cancellation of claims 16, 18 and 34 and the amendment to claim 37.

The rejection of claims 1, 11-12, 14-19, 23-32, 48-49 and 52-55 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for neutralizing bispecific fusion proteins capable of binding to an inducing site on gp120 (CD4 binding site) thereby exposing an induced epitope of gp120 (co-receptor binding site) and a second binding domain capable of forming a neutralizing complex with the induced epitope wherein the first binding domain is sCD4 (soluble CD4) and the second binding domain is SCFv(17b), does not reasonably provide enablement for neutralizing bispecific fusion proteins capable of binding to an inducing site on gp120 (CD4 binding site) thereby exposing an induced epitope of gp120 (co-receptor binding site) and a second binding domain capable of forming a neutralizing complex with the induced epitope wherein the first binding domain is anything other than sCD4 (soluble CD4) and/or the second binding domain is anything other than SCFv(17b) is withdrawn in light of the amendment to claim 1 and the cancellation of claims 11-12, 14-18 and 55.

The rejection of claim 55 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn. Cancellation of said claim has rendered the rejection moot.

The rejection of claim 33 under 35 U.S.C. 112, second paragraph, for lacking sufficient antecedent basis for the limitation "functional recombinant" is withdrawn in light of the amendment thereto.

The rejection of claim 37 under 35 U.S.C. 112, second paragraph, as being vague and indefinite by being dependent on a non-elected claim is withdrawn in light of the amendment thereto.

The rejection of claim 34 rejected under 35 U.S.C. 112, second paragraph, is withdrawn. Cancellation of said claim has rendered the rejection moot.

The rejection of claims 1-12, 14-18, 34 and 55 under 35 U.S.C. 103(a) as being unpatentable over Traunecker et al. (International Journal of Cancer, Supplement 7, 1992, pages 51-52 – IDS-6) in view of Sullivan et al. (Journal of Virology, Vol. 72, No. 6, 1998, pages 4694-4703 – IDS-6) is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 1-12, 14-18, 34 and 55 under 35 U.S.C. 103(a) as being unpatentable over Traunecker et al. (International Journal of Cancer, Supplement 7, 1992, pages 51-52 – IDS-6) in view of Thali et al. (Journal of Virology, Vol. 67, No. 7, 1993, pages 3978-3988 – IDS-6) is withdrawn. Cancellation of said claims has rendered the rejection moot.

Claim Rejections *Maintained and New Grounds of Rejection*

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 19, 23-33, 48-49 and 52-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the single-chain Fv SCFv(17b) is required in order to practice the claimed invention. The deposit of said biological materials is considered by the Examiner to be necessary for the enablement of the current invention (see 37 CRF 1.808(a)).

If the deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty *and* that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit, or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

1) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

2) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent; and

3) the deposits will be maintained for a term of at least thirty (30) years from the date of the deposit or for the enforceable life of the patent or for a period of at least five (5) years after the most recent request for the furnishing of a sample of the deposited material, whichever is longest; and

4) a viability statement in accordance with the provisions of 37 CFR 1.807; and

5) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CRF 1.809(d) should be added to the specification. See 37 CFR 1.803 – 1.809 for additional explanation of these requirements.

The rejection of claim 49 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record.

Applicant argues:

1. The specification describes making pharmaceutical compositions comprising bispecific fusion proteins.

2. The specification describes the clinical use of bispecific fusion proteins.

3. The clinical use of sCD4-SCFv(17)b is described on page 27, lines 6-10.

4. The specification discloses that sCD4-SCFv(17)b strongly inhibits HIV-1 Env-mediated cell fusion.

5. Compliance with the enablement requirement does not turn on whether an example is disclosed.

6. An example may be working or prophetic.

7. The specification discloses many prophetic examples of the *in vivo* use of the sCD4-SCFv(17)b bispecific fusion protein.

Applicant's arguments have been full considered and deemed non-persuasive.

The aforementioned claim is drawn to pharmaceutical compositions comprising the sCD4-SCFv(17)b bispecific fusion protein.

With regard to Point 1, the rejection is based on the lack of guidance with regard to the use of the claimed composition, not the making of said composition.

With regard to Points 2-3 and 5-8, the specification discloses prophetic statements about possible applications including its use to "prevent" HIV infection before virus exposure (see page 27, lines 17-20). To date, there is no prophylaxis for HIV in man. It should be noted that the prophylactic use of the claimed fusion protein is encompassed by the instant claim. Consequently, since the specification is silent on how such a composition would be used and

equally silent on the efficacy of said compositions it cannot be enabling for the use of pharmaceutical compositions comprising the sCD4-SCFv(17)b bispecific fusion protein.

With regard to Point 4, *in vitro* effects do not translate into *in vivo* efficacy.

Therefore, as outlined previously, people of skill in the art require evidence that a benefit can be derived by the application of a given substance. The specification, as filed, does not set forth that the claimed compositions provide any sort of therapeutic effect in any model system that can be applied (or extrapolated) to humans or higher mammals (or in humans themselves). The specification describes (prophetically, in most instances) how a given fusion protein composition can be made but is silent on its therapeutic use. While the skill in the art of immunology is high, to date, prediction of a therapeutic benefit (effect) for any given composition is quite unpredictable. Moreover, while one may know how to make the composition (as is the case with sCD4-SCFv(17b)), no evidence has been provided that illustrates or even suggest that the claimed pharmaceutical compositions are capable of eliciting a beneficial response, one of skill in the art has not been taught to use the claimed composition as a pharmaceutical, as is required by the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1, 19, 23-3348-49 and 52-54 under 35 U.S.C. 103(a) as being unpatentable over Traunecker et al. (International Journal of Cancer, Supplement 7, 1992, pages 51-52 – IDS-6) in view of Sullivan et al. (Journal of Virology, Vol. 72, No. 6, 1998, pages 4694-4703 – IDS-6) is maintained for reasons of record.

The instant claims are drawn to for neutralizing bispecific fusion proteins capable of binding to an inducing site on gp120 (CD4 binding site) thereby exposing an induced epitope of gp120 (co-receptor binding site) and a second binding domain capable of forming a neutralizing complex with the induced epitope wherein the first binding domain is sCD4 and the second

binding domain is SCFv(17)b the first and second binding domains are separated by a linker (optionally, at least one occurrence of SEQ ID NO:1 or SEQ ID NO:2).

Applicant argues:

1. Traunecker et al. do not disclose a bispecific fusion protein that can bind tow different sites on the same molecule.

2. Sullivan et al. does not overcome the deficiency Traunecker et al. hence the combination of the references does not provide all the limitations of the instant invention.

3. There is no indication in either reference that the cited references could or should be combined.

As outlined previously, Traunecker et al. disclose single chain bispecific reagents (fusion proteins) wherein the first binding domain is derived from soluble CD4 (sCD4) and the second binding domain is derived from the Fv domain of an anti-CD3 antibody. Traunecker et al. further the two binding domains are joined by a polypeptide linker. Traunecker et al. differs from the instant invention in that they do not explicitly disclose the use of antibody binding domains that bind to an induced epitope of gp120 (i.e. 17b) as the second binding domain nor do they disclose the use of linkers with the sequence of either SEQ ID NO:1 or SEQ ID NO:2. Sullivan et al. disclose the use of sCD4 in conjunction with neutralizing antibodies (17b and CG10) to inhibit (neutralize) the activity of gp120 (see abstract). Sullivan et al. further disclose that the 17b and CG10 binding epitopes are exposed by the binding of sCD4 to gp120 (see abstract, page 4695 and pages 4696-4697). Moreover, Sullivan et al. disclose that sCD4 dramatically enhanced the neutralizing ability of the 17b and CG10 antibodies (see pages 4700-4701). Finally, Sullivan et al. disclose that the gp120 binding epitopes for 17b and CG10 are well conserved and are present

on a multitude of wild-type HIV-1 isolates (see pages 4695 and 4697-4699). Consequently, it would have been obvious to substitute the anti-CD3 binding domains in the sCD4-FvCD3 bispecific fusion protein disclosed by Traunecker et al. with the binding domains of either the 17b or CG10 antibody disclosed by Sullivan et al. in order to take advantage of the ability of the resulting antibodies to neutralize the infectivity (gp120 activity) of a wide variety of wild-type HIV-1 isolates and the reduced number of escape mutants that would result in any *in vivo* application of the bispecific fusion protein disclosed by Traunecker et al. Moreover, the bispecific fusion proteins of Traunecker et al. "provide efficient transport of these molecules as cell-bound entities to the sites of infection and thus the functional half-lives of these molecules can be made greater than those of free soluble molecules (see page 52). Finally, an sCD4-17b or sCD4CG10 fusion protein would eliminate the increase in virus entry or syncytium formation sometimes associated with sCD4 alone (see Sullivan et al. page 4695). Moreover, the resulting fusion protein would have the same binding properties as the instant invention since they comprise the same binding domains. Hence, contrary to Applicants assertion to the contrary, the combined references meet all the limitations of the instant claims. One of skill in the art would have had high expectation of success since Traunecker et al. disclose that their "approach to design single-chain molecules can be applied more generally". It should be noted that linkers disclosed by Traunecker et al. do not have the sequence of either SEQ ID NO:1 or SEQ ID NO:2. However, the use of linkers is well known in the art and, in the absence of evidence to the contrary, the use of linkers with the sequence of either SEQ ID NO:1 or SEQ ID NO:2 would be obvious to one of ordinary skill in the art when maintaining the spatial orientation of CD4 and either the 17b or CG10 binding domains with their respective gp120 binding epitopes. It would

be equally obvious to one of ordinary skill in the art to package the aforementioned claimed fusion protein in a kit bundled with instructions in order to facilitate ease of use and reduce cost.

Claims 1, 11-12, 14-19, 23-34, 37, 48-49 and 52-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Traunecker et al. (International Journal of Cancer, Supplement 7, 1992, pages 51-52 – IDS-6) in view of Thali et al. (Journal of Virology, Vol. 67, No. 7, 1993, pages 3978-3988 – IDS-6).

The instant claims are drawn to for neutralizing bispecific fusion proteins capable of binding to an inducing site on gp120 (CD4 binding site) thereby exposing an induced epitope of gp120 (co-receptor binding site) and a second binding domain capable of forming a neutralizing complex with the induced epitope wherein the first binding domain is sCD4 and the second binding domain is SCFv(17)b the first and second binding domains are separated by a linker (optionally, at least one occurrence of SEQ ID NO:1 or SEQ ID NO:2).

Applicant argues:

1. Traunecker et al. do not disclose a bispecific fusion protein that can bind tow different sites on the same molecule.

2. Sullivan et al. does not overcome the deficiency Traunecker et al. hence the combination of the references does not provide all the limitations of the instant invention.

3. There is no indication in either reference that the cited references could or should be combined.

As outlined previously, Traunecker et al. disclose single chain bispecific reagents (fusion proteins) wherein the first binding domain is derived from soluble CD4 (sCD4) and the second

binding domain is derived from the Fv domain of an anti-CD3 antibody. Traunecker et al. further the two binding domains are joined by a polypeptide linker. Traunecker et al. differs from the instant invention in that they do not explicitly disclose the use of antibody binding domains that bind to an induced epitope of gp120 (i.e. 17b) as the second binding domain nor do they disclose the use of linkers with the sequence of either SEQ ID NO:1 or SEQ ID NO:2. Thali et al. disclose the use of sCD4 in conjunction with neutralizing antibodies (17b and 48d) to inhibit (neutralize) the activity of gp120 (see abstract). Thali et al. further disclose that the 17b and 48d binding epitopes are exposed by the binding of sCD4 to gp120 (see abstract and page 3983-3984). Moreover, Thali et al. disclose that the gp120 binding epitopes for 17b and 48d are well conserved and are present on a multitude of wild-type HIV-1 isolates (see page 3984). Consequently, it would have been obvious to substitute the anti-CD3 binding domains in the sCD4-FvCD3 bispecific fusion protein disclosed by Traunecker et al. with the binding domains of either the 17b or 48d antibody disclosed by Thali et al. in order to take advantage of the ability of said antibodies to neutralize the infectivity (gp120 activity) of a wide variety of wild-type HIV-1 isolates and the reduced number of escape mutants that would result in any *in vivo* application of the bispecific fusion protein disclosed by Traunecker et al. Moreover, the bispecific fusion proteins of Traunecker et al. "provide efficient transport of these molecules as cell-bound entities to the sites of infection and thus the functional half-lives of these molecules can be made greater than those of free soluble molecules (see page 52). Moreover, the resulting fusion protein would have the same binding properties as the instant invention since they comprise the same binding domains. Hence, contrary to Applicants assertion to the contrary, the combined references meet all the limitations of the instant claims. One of skill in the art would

have had high expectation of success since Traunecker et al. disclose that their "approach to design single-chain molecules can be applied more generally". It should be noted that linkers disclosed by Traunecker et al. do not have the sequence of either SEQ ID NO:1 or SEQ ID NO:2. However, the use of linkers is well known in the art and, in the absence of evidence to the contrary, the use linkers with the sequence of either SEQ ID NO:1 or SEQ ID NO:2 would be obvious to one of ordinary skill in the art when maintaining the special orientation of CD4 and either the 17b or 48d binding domains with their respective gp120 binding epitopes. It would be equally obvious to one of ordinary skill in the art to package the aforementioned claimed fusion protein in a kit bundled with instructions in order to facilitate ease of use and reduce cost.

Conclusion

No claim is allowed.

Claim 37 is free of the art of record since SEQ ID NO:4 is free of the art of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Robert A. Zeman
June 2, 2004